mixtures analyzed by comparison with the standard curves at suitable wave lengths. The values cited are approximate only. We have checked several results qualitatively by formation of the phenyl urethans. Our qualitative results checked the infrared results about as well as could be expected. [c] Raney nickel prepared as described in "Organic Syntheses," Vol. XXI, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 15. [d] Presence of this component judged qualitatively either by $n^{20}D$ and b. p. or by formation of phenyl urethan. [e] Attempted hydrogenolysis by adsorbed hydrogen as in desulfurization reactions. [f] Raney nickel prepared as by Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946). [g] Average of two identical runs, per cent. calculated from infrared analysis; see *b*. [h] Reductions with added phosphoric acid much more sluggish. [i] Higher pressure to attempt speedier reduction, however, still sluggish. [j] Some compound other than styrene oxide was also present. [k] At the higher temperature the ring reduced yielding cyclohexane derivatives.

gave mainly primary alcohol but in the presence of as little as 0.1 g. of acid or base in over 100 cc. of solution primary alcohol formation was markedly decreased.

## Experimental

1-Decene was converted to 1,2-epoxydecane, b. p. 82–83.5° at 10 mm., by reaction with peracetic acid.[6] 1-Decanol, b. p. 111.5–113.5° at 11 mm., and 2-decanol, b. p. 104.5–106.0° at 13 mm., were prepared by treating *n*-octylmagnesium bromide with ethylene oxide and acetaldehyde. The corresponding phenylurethans melted at 58.5–59.5 and 37–38°.

A commercial sample of styrene oxide (Dow) was rectified to yield pure styrene oxide, b. p. 81.5° at 15 mm., $n^{20}D$ 1.5350. Pure rectified α-phenylethyl alcohol, $n^{20}D$ 1.5272, formed a phenylurethan which melted at 93–94° and pure rectified β-phenylethyl alcohol, $n^{20}D$ 1.5325, formed a phenylurethan which melted at 78–79°.

**General Procedure for Catalytic Reduction.**—A mixture of 10 g. of 1,2-epoxydecane, 2.5 g. of wet catalyst (wet with absolute alcohol but containing 1 g. dry weight of catalyst), and 115 cc. of absolute alcohol was reduced in standard high pressure equipment. After reduction the catalyst was removed by filtration and washed well with solvent. The solvent was stripped and the residue was vacuum distilled without attempting fractionation. The entire distillate which usually amounted to 8.5 g. was weighed and its index of refraction determined. Part of the sample was then sealed in a glass ampoule and sent to the Goodrich Company for infrared analysis. In several cases the reaction mixture was treated with excess phenyl isocyanate and the melting point of the mixed phenylurethans taken. For runs which analysis indicated to consist of mainly primary alcohol there was no difficulty in isolating fairly good yields of the phenylurethan of the primary alcohol. The same was true for the phenylurethan of the secondary alcohol in mixtures rich in this compound. From reaction mixtures which analysis indicated a mixture of about equal parts, no pure urethan was isolated.

In the catalytic reductions involving styrene oxide conditions were the same as above except that only 100 cc. of alcohol was used.

**Chemical Reduction of 1,2-Epoxydecane.**—To a solution of 10 g. of epoxide in 100 cc. of water and 200 cc. of ethyl alcohol was added 500 g. of 3% sodium amalgam. After standing at room temperature for sixteen hours with occasional shaking and neutralization of excess alkali with carbon dioxide the product was isolated as above. The reduction, incomplete under these conditions, yielded mainly 2-decanol.

When 1,2-epoxydecane was treated with an equivalent amount of lithium aluminum hydride[5] in dry ether the product consisted exclusively of 2-decanol except for some unreacted epoxide.

## Summary

On catalytic hydrogenation over Raney nickel 1,2-epoxydecane yields mainly 1-decanol. In the presence of small amounts of sodium hydroxide, however, mainly 2-decanol results. With sodium amalgam and lithium aluminum hydride 2-decanol is the main product.

Styrene oxide yields β-phenylethyl alcohol exclusively on catalytic reduction over Raney nickel either with or without added sodium hydroxide. The addition of phosphoric acid retards the reduction markedly and causes complications but primary alcohol is still the main product.

(6) Swern, Billen and Scanlan, THIS JOURNAL, **68**, 1504 (1946).

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[CONTRIBUTION FROM THE CHEMICAL DIVISION OF THE PROCTER & GAMBLE CO.]

# The Polymorphism of Saturated 1,3-Diglycerides

BY F. J. BAUR, F. L. JACKSON, D. G. KOLP AND E. S. LUTTON

## Introduction

Malkin, Shurbagy and Meara[1] have described the polymorphism of both even and uneven monacid saturated 1,3-diglycerides of the series dicaprin through distearin. They have reported two sets of long spacings which give two straight lines if spacings are plotted against chain length. For the lower members, including dilaurin (LL) and dimyristin (MM), the greater long spacings were reported to be associated with short spacings of a type specified as "a"; the lesser long spacings were associated with short spacings of type "b." In the case of dipalmitin (PP) and distearin (SS) only the lesser long spacings were observed and these were associated, oddly, with "a" instead of "b" short spacings.

In the present paper are reported results of a reexamination of the even diglycerides, dilaurin through distearin, in the course of which two long spacing values were found uniformly for each compound, and the lesser and greater long spacings were respectively associated with "a" and with "b" type short spacings.

## Experimental

The dipalmitin used in this study was prepared according to the directed rearrangement procedure described by Eckey and Formo.[2] Cottonseed oil stearin containing approximately 35% of saturated fatty acids was rearranged

(1) Malkin, Shurbagy and and Meara, *J. Chem. Soc.*, 1409 (1937).

(2) Eckey and Formo, *J. Am. Oil Chem. Soc.*, **26**, 207 (1949).

TABLE I

CONSTANTS FOR 1,3-DIGLYCERIDES

| | M. p., °C. | Hydroxyl value Found | Hydroxyl value Calcd. | Saponification value Found | Saponification value Calcd. | % monoglyceride[4] Found | % monoglyceride[4] Calcd. |
|---|---|---|---|---|---|---|---|
| Distearin | 78.2, 78[1] | 89 | 90 | 179.4 | 179.7 | 0.1 | 0.0 |
| Dipalmitin | 72.9, 72.5[1] | 98 | 99 | 197.3 | 197.2 | .2 | .0 |
| Dimyristin | 66.5, 65.5[1] | 109 | 109 | 216.8 | 218.5 | <.1 | .0 |
| Dilaurin | 56.8, 56.5[1] | 119 | 123 | 245.7 | 245.7 | <.1 | .0 |

with 8% glycerol, representing a slight excess over the theoretical quantity required to convert all triglycerides to diglycerides. The crude diglyceride was purified by 6 recrystallizations from hexane and hexane–alcohol. The distearin, dimyristin, and dilaurin were prepared by a modification of this procedure.[3] Constants for the diglycerides are given in Table I.

Thermal examination was carried out in the manner of previous investigations in this Laboratory[5] but with one additional procedure to register a "cloud point." For this observation sealed 1-mm. capillary tubes containing the diglyceride were lowered in temperature about 2° per minute until the temperature of clouding was observed. This value is reproducible within about 0.5°. The test was run to see whether diglycerides like mono- and triglycerides show a supercooling limit near their lowest m. p. level. Such behavior would indicate the occurrence of alpha-type forms. "Rapid c. m. p." was determined on a freshly chilled sample by a "thrust-in" technique and "regular c. m. p." by raising the bath temperature 0.2° per minute.

X-Ray diffraction patterns were obtained as previously described[6] on chilled, aged and solvent crystallized samples.

Thermal and diffraction data are recorded in Tables II and III.

TABLE II

THERMAL DATA FOR 1,3-DIGLYCERIDES

| Thermal point | Distearin | Dipalmitin | Dimyristin | Dilaurin |
|---|---|---|---|---|
| Cloud point (beta-a?) | 73.5 | 67.0 | 60.5 | 50.0 |
| Rapid c. m. p. (beta-a) | 77.2 | 71.8 | 64.3 | 54.0 |
| Regular c. m. p. (beta-a and beta-b) | 78.2 | 72.9 | 66.5 | 56.8 |
| Time required for transformation (beta-a to beta-b) at reg. c. m. p. −2° | 5 hr. | 2 hr. | 1 min. | 1–5 min. |

## Discussion

The reëxamination of this glyceride series reveals a close resemblance of the members to each other in polymorphic behavior as would be expected from their homologous molecular structures. Previously reported discontinuities between dimyristin and dipalmitin[1] were not confirmed.

Two forms were obtained for each diglyceride, each form having a strong 4.6 Å. short spacing line. A nomenclature has been adopted which is consistent on one hand with that established for triglycerides[6] (and stemming originally from the work of Malkin) and on the other hand with Malkin's distinction between "a" and "b" short spacing types for diglycerides.[1] Both forms are labeled "beta" on the basis of their strong 4.6 spacings, and distinguished as "a" or "b" on the basis of other important short spacings. Thus the two different forms here reported are named as follows—beta-a with characteristic short spacings 4.6 Å. VS, 3.9 M, 3.7 S; beta-b with characteristic short spacings 4.6 Å. VS, 3.75 $S^+$. This corresponds to the nomenclature of Sidhu and Daubert[7] for mixed diglycerides.

A feature of significance in clarifying the polymorphism of these compounds is illustrated in Fig. 1. In contrast to the data of Malkin, *et al.*,[1] it is shown that the beta-a short spacings are uniformly associated with the lesser long spacing for each of the four homologs; similarly beta-b is associated with the greater long spacing.

Beta-a is invariably obtained on cooling a melt. It is extremely stable at room temperature, in no case having been observed to transform at that level. It transforms to beta-b at a temperature within 2° of the melting point at rates which are, in general, inversely related to chain length. Rate of transformation is controlled by purity of sample, increasing with purity of constituent saturated acids and with increasing number of crystallizations. The corresponding monoglyceride, however, actually promotes transformation while triglyceride exerts a negligible retarding effect. It would seem that mixed diglycerides might be responsible for the slowing down of conversion in less pure samples. Such mixed glycerides are thought to account for the slower transformation rate of dilaurin relative to dimyristin, indicated in Table II. Beta-a is frequently obtained by solvent crystallization, being favored by lower temperatures, by more polar solvents and by presence of impurities (not monoglycerides), but the conditions are not clearly established.

Beta-b, as has been said, may be obtained from beta-a. Since the tranformation has not been observed to be reversible, beta-b appears to be the only thermodynamically stable form. It is favored in solvent crystallization by higher temperatures and less polar solvents. (Beta-b was not reported for dipalmitin and distearin by Malkin, *et al.*[1])

Beta-a, when formed from the melt by chilling, gives a "rapid c. m. p." (by "thrust-in" technique) about 2° below the solvent crystallized m. p. This signifies a certain degree of imperfection of the rapidly formed crystallites. A "regular c. m. p." on a chilled sample is within 0.5° of the maximum m. p. value and solvent crystallized beta-a appears

(3) To be reported.

(4) Handschumacher and Linteris, *J. Am. Oil Chem. Soc.*, **24**, 143 (1947).

(5) Lutton, Jackson and Quimby, THIS JOURNAL, **70**, 2441 (1948).

(6) Lutton, THIS JOURNAL, **70**, 248 (1948).

(7) Sidhu and Daubert, *ibid.*, **68**, 2603 (1946).

TABLE III

X-RAY DIFFRACTION DATA FOR 1,3-DIGLYCERIDES IN Å.

| *hkl* | Beta-a Distearin | Beta-a Dipalmitin | Beta-a Dimyristin | Beta-a Dilaurin | Beta-b Distearin | Beta-b Dipalmitin | Beta-b Dimyristin | Beta-b Dilaurin |
|---|---|---|---|---|---|---|---|---|
| | | | | Long spacings | | | | |
| 001 | 50 VS | 44 VS | 40.5 VS | 35 VS | 51.3 VS | 47.0 VS | 42.7 S | 36.7 VS |
| 002 | 25.1 M | 22.2 M | 20.3 M | 17.7 W | 26.2 M | 23.8 M | 21.2 W | 18.8 S |
| 003 | 16.7 S+ | 14.9 S | 13.5 S | 11.8 M | 17.5 S | 15.9 S | 14.2 M | 12.6 VS |
| 004 | | | 10.2 W | 8.89 W | | | 10.49 W | 9.41 M |
| 005 | 10.0 VW | 8.9 W | | | 10.6 W | 9.48 VW | | |
| 006 | 8.37 VW+ | 7.5 W+ | 6.88 M | 5.89 W | 8.5 W | 7.86 M | 7.02 W | 6.23 W |
| 007 | | | | | | | | 5.30 W |
| 008 | 6.28 VW | 5.6 W+ | | | 6.6 W | 5.97 W | | |
| Av. d | 50.2 | 44.7 | 40.6 | 35.4 | 52.8 | 47.4 | 42.4 | 37.5 |
| | | | | Short spacings | | | | |
| | | | | | 5.38 VW | | 5.68 W | |
| | 4.61 VS | 4.60 VS | 4.58 S | 4.58 S | 4.59 VS− | 4.58 VS | 4.55 S | 4.55 M |
| | 4.21 VW | 4.06 VW | 4.15 VW | 4.11 VW | 4.14 W | | 4.13 VW | |
| | 3.90 S | 3.88 M | 3.91 M | 3.89 M | 3.74 VS | 3.75 VS | 3.74 S | 3.70 S |
| | 3.71 S+ | 3.72 S+ | 3.73 S | 3.68 S | 2.52 W | 2.69 W | 3.44 VW | 3.42 VW |
| | 3.39 VW | 3.31 VW | 2.79 VW | 3.39 W | 2.44 W | 2.62 W | 3.31 VW | 2.42 W |
| | 2.80 VW | 2.77 VW | 2.53 W | 2.75 W | 2.31 VW | 2.45 M | 3.11 VW | 2.20 VW |
| | 2.55 W+ | 2.50 M | 2.44 VW | 2.50 W | 2.18 W | 2.40 W | 2.91 VW | 2.13 VW |
| | 2.44 VW | 2.29 W | 2.38 VW | 2.41 W | | 2.33 W− | 2.64 VW | |
| | 2.30 VW | 2.23 W | 2.24 W | 2.30 W | | 2.26 W | 2.48 VW | |
| | | | | 2.25 W | | 2.17 W+ | | |

to melt as high as beta-b. (Of course, it may be that beta-a transforms to beta-b very rapidly near the m. p.)

It is a matter of speculative interest, at least, that certain analogies exist between the diffraction patterns of saturated di- and triglycerides. Thus, as pointed out by Malkin, *et al.*,[1] both beta-a diglyceride forms and beta-2 triglyceride forms show 4.6, 3.9, and 3.7 Å. short spacings (4.6 strongest). Likewise, beta-b (diglyceride) and beta-3 (triglyceride) have 4.6 and 3.75 Å. short spacings (3.75 strongest) in common. Moreover, just as beta-b forms exceed corresponding beta-a forms by about 2 Å. in long spacings, so beta-3 long spacings (when compared on a double-chain length basis) are 2 Å. greater than beta-2 values.[8] It should be noted, however, that beta-a long spacings exceed corresponding beta-2 long spacings by 5 Å.

A notable feature of these diglycerides is their apparent lack of alpha forms (single strong spacing near 4.2 Å.). While each compound shows approximately 5° of supercooling, in no case is a m. p. observable in the neighborhood of the supercooling limit. Therefore one characteristic common to the alpha forms of 1-mono- and triglycerides, namely, the close agreement of supercooling limit and lowest melting point, is here lacking. This fact and failure to obtain alpha patterns show that if alpha forms do occur at all for these diglycerides, they are extremely fleeting.

**Acknowledgment.**—The authors wish to express their appreciation to those of this laboratory who have assisted in the experimental work.

(8) In the terms of a previous publication,[6] $2/3\ (L\beta)_T' = (L\beta)_D + 2$.

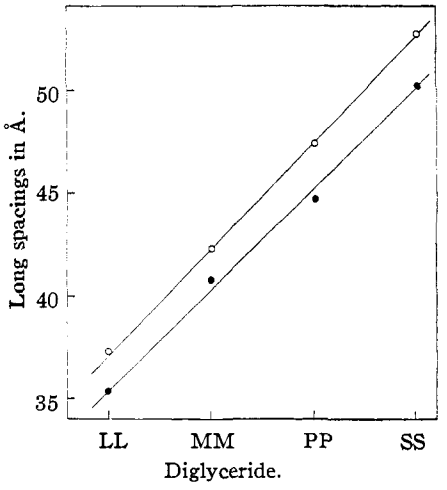


Fig. 1.—Diglyceride long spacings: ●, beta-a (metastable); O, beta-b (stable).

## Summary

A reëxamination of the polymorphism of the even, saturated 1,3-diglycerides, dilaurin through distearin, has revealed a uniformity of behavior which does not confirm the discontinuities reported by Malkin, *et al.*[1]

Each diglyceride has two forms, both classified as beta-like on the basis of strong 4.6 Å. spacings. After a suggestion of Malkin, the two forms are called beta-a and beta-b and are readily distinguishable by differences in short spacings in the

3.8 Å. region. For a given glyceride the beta-b long spacing exceeds that of beta-a by about 2 Å.

Beta-a is invariably obtained from the melt and may sometimes be obtained by solvent crystallization. Highly stable at room temperature, it transforms to beta-b near the m. p. Beta-b, apparently the only thermodynamically stable form, is obtained by transformation of beta-a and commonly by solvent crystallization.

It is notable that no alpha-like patterns were observed, although they are readily obtained with 1-mono- and triglycerides.

Purely on the basis of similarity in X-ray diffraction patterns, it is suggested that a structural similarity may exist between beta-a diglyceride forms and beta-2 triglyceride forms and between beta-b (diglyceride) and beta-3 (triglyceride).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# Sulfur-Containing Amines. VIII.[1] Local Anesthetics. III

BY R. O. CLINTON, U. J. SALVADOR AND S. C. LASKOWSKI

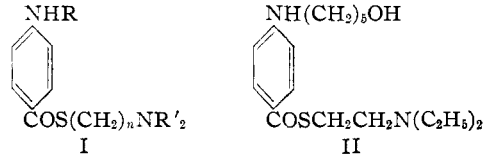
In extending previous investigations[2,3] there have been prepared a number of dialkylaminoalkyl thiol esters derived from various nuclei, for testing as local anesthetics.

In comparison to the oxygen analogs, very few local anesthetics of the dialkylaminoalkyl thiol ester type have appeared in the literature. Karjala and McElvain[4] have recorded the preparation of 3-(2-methylpiperidyl-1)-propyl thiolbenzoate hydrochloride, the thiol analog of Metycaine, by a four step synthesis *via* 3-bromopropyl thiolbenzoate. Lischer and Jordan[5] prepared a short series of 3-dialkylaminopropyl 4-aminothiolbenzoate hydrochlorides *via* 3-chloropropyl 4-nitrothiolbenzoate, in which the terminal tertiary amino group varied from diethylamino to diamylamino. Sergievskaya and Kropacheva[6] investigated a series of diethylamino-ethyl, -propyl and -butyl naphthalene-1-thiolcarboxylates and 4-aminonaphthalene-1-thiolcarboxylates. These compounds were reported by the authors to possess high anesthetic potency without irritation or other untoward effects. Further, a patent[7] reported the properties of three diethylaminoethyl 4-alkoxythiolbenzoate hydrochlorides, prepared by the action of a 4-alkoxybenzoyl chloride on 2-bromoethanethiol and subsequent reaction with a secondary amine.

An important advantage of simple local anesthetics of the types of Apothesine and Metycaine is the lack of PABA interference in clinical usage. It was felt in the present work that simple thiolbenzoates and thiolcinnamates might, while satisfying this condition, in addition possess lowered toxicity while retaining activity. Certain examples of these types have been prepared.

A few additional examples of diphenylthiolacetates[3,8] were prepared, since pharmacological screening has indicated that these compounds are strong local anesthetics, in analogy with other antispasmodics of related type.

A further interesting type of thiol ester is that related to Thiocaine.[2,9] This ester possesses a high therapeutic index in relation to Procaine[9]; similar high activity in analogous types is reported by Lischer and Jordan.[5] This series has therefore been widely extended, through variation of the dialkylaminoalkyl grouping. Of greater interest, insofar as activity is concerned, are the dialkylaminoalkyl thiol esters, (I), related to Tetracaine. A series of these compounds was prepared,




I II

either by reductive alkylation of the parent 4-aminothiolbenzoate, or by the reaction between a dialkylaminoalkanethiol and a 4-alkylaminobenzoyl chloride hydrochloride. A new example of this type was prepared by using 5-hydroxypentanal as the alkylating agent, to yield the compound II. The effect on activity of the inclusion of a hydroxyl group in this position of the nucleus has not been previously determined.

Several thiol esters derived from 2-butyloxyquinoline-4-carboxylic acid were also prepared, to determine whether the high toxicity and irritation associated with the Nupercaine series could be decreased through inclusion of a sulfur linkage in the ester group. Further, two examples of the 4-alkoxythiolbenzoate type[7] were prepared from the acid chloride and a thiol, to enable evaluation in comparison with the 4-aminothiolbenzoate analogs.

(1) Paper VII, Clinton, Salvador and Laskowski, THIS JOURNAL, **71**, 1300 (1949).

(2) Albertson and Clinton, *ibid.*, **67**, 1222 (1945).

(3) Clinton and Salvador, *ibid.*, **68**, 2076 (1946).

(4) Karjala and McElvain, *ibid.*, **55**, 2966 (1933).

(5) Lischer and Jordan, *ibid.*, **59**, 1623 (1937).

(6) Sergievskaya and Kropacheva, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 1737 (1940) (*C. A.*, **35**, 4003 (1941)).

(7) Harris and Braker, U. S. Patent 2,342,142.

(8) Richardson, U. S. Patent 2,390,555 (1945); Dupré, Lévy and Tchoubar, *Compt. rend. soc. biol.*, **140**, 477 (1946); Tchoubar and Letellier-Dupré, *Bull. soc. chim.*, 792 (1947).

(9) Hansen and Fosdick, THIS JOURNAL, **55**, 2872 (1933); *J. Pharmacol.*, **50**, 323 (1934); Nolle, *Farm. i. Farmacol.* (*U. S. S. R.*), (1937) No. 2, 1 [*C. A.*, **34**, 3820 (1940)].